Comparative effects of quinine and quinidine on glucose metabolism in healthy volunteers

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1 To investigate the relative effects of quinine and quinidine on glucose metabolism, 11 healthy males aged 17–32 years were given three separate 1 h intravenous infusions; normal saline alone, quinine dihydrochloride 10 mg base kg⁻¹ body weight (BW) in normal saline, and quinidine dihydrochloride 10 mg base kg⁻¹ BW in normal saline. A constant infusion of 5 mg glucose kg⁻¹ ideal BW min⁻¹ was given for 1 h before and during each study.

2 Assessment of pancreatic beta cell function and tissue insulin sensitivity from plasma glucose and insulin concentrations at the end of the first hour using the Continuous Infusion of Glucose with Model Assessment (CIGMA) technique confirmed normal glucose tolerance for each subject on each test day.

3 Plasma glucose concentrations at 1 h were similar to those at 2 h. There was no significant difference between the plasma glucose profiles during the three infusion regimes ($P > 0.05$). Plasma insulin rose significantly during the second hour ($P < 0.0001$); increments after quinine (geometric mean $[-1 \text{ s.d.} - +1 \text{ s.d.}]$; 47.0 [27.8–79.4] $\mu\text{U l}^{-1}$) were significantly greater than those after quinidine (19.8 [6.1–65.2] $\mu\text{U l}^{-1}$) and saline (7.5 [0–21.5] $\mu\text{U l}^{-1}$; $P < 0.05$). Plasma quinine concentrations at the end of the infusion ($6.5 \pm 4.4 \text{ mg l}^{-1}$) correlated with insulin increments during the second hour ($r = 0.662$, $P = 0.028$) and were significantly greater than those of quinidine ($3.0 \pm 0.8 \text{ mg l}^{-1}$; $P < 0.05$). Plasma concentrations of free (unbound) quinine at 2 h ($0.55 \pm 0.28 \text{ mg l}^{-1}$) also correlated with insulin increments ($r = 0.705$, $P = 0.015$) but were significantly lower than those of free quinidine ($0.91 \pm 0.36 \text{ mg l}^{-1}$, $P < 0.05$).

4 These data suggest that quinine is a more potent stimulus to insulin secretion than quinidine in healthy subjects.

Keywords Quinine quinidine glucose insulin

Introduction

Both quinine and its diastereoisomer quinidine are widely used drugs. Quinine is the treatment of choice for chloroquine-resistant falciparum malaria (W.H.O., 1986), is commonly prescribed for nocturnal cramps, and is also widely used as a food and beverage flavouring. Quinidine is a well-established anti-arrhythmic

drug used to treat both ventricular and supraventricular arrhythmias, and also has powerful antimalarial activity (Fletcher, 1925; Sanders & Dawson, 1932). However, because of its potentially greater cardiotoxic effects, the use of quinidine in the treatment of *Plasmodium falciparum* infections has hitherto been limited to

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situations where quinine is unavailable (Miller *et al.*, 1989; White, 1987).

Both quinine and quinidine are known to stimulate insulin secretion at therapeutic blood concentrations (Phillips *et al.*, 1986; White *et al.*, 1983) leading to hypoglycaemia (Harats *et al.*, 1984; Looareesuwan *et al.*, 1985; Okitolonda *et al.*, 1987; White *et al.*, 1983). However, little is known of the relative effects of these two drugs on the pancreatic beta cell. As there is evidence of increasing resistance to the antimalarial action of quinine (Bunnag & Harinasuta, 1984; Chongsuphajaisiddhi *et al.*, 1981), the use of quinidine is likely to increase. It is, therefore, important to determine the relative risks of hyperinsulinaemia and consequent hypoglycaemia resulting from administration of the two drugs.

Although malaria *per se* can profoundly influence antimalarial drug disposition, changes in clinical status preclude within-patient drug comparisons (White, 1985). Because of this, we have examined the effects of quinine and quinidine on glucose metabolism in healthy volunteers using a simple crossover design.

Methods

Subjects

Eleven healthy Thai males aged between 17 and 32 years and with an average body mass index of 21.6 kg m^{-2} (absolute range 17.6–27.7) were recruited. The subjects were all urban dwellers with no history of malnutrition who were neither known to be diabetic nor had a family history of diabetes. No subject was taking regular medication at the time of study. All subjects gave fully informed consent to participation in the study which was approved by the Ethics Review Sub-Committee of the Research Committee of the Ministry of Public Health, Bangkok, Thailand.

Methods

Each subject was asked to attend after an overnight fast on three occasions separated by at least a week. A standard 2 h protocol was followed on each test day. During the first hour, glucose alone at 5 mg kg^{-1} ideal body weight (IBW; Metropolitan Life Tables, 1959) min^{-1} was administered by constant intravenous infusion using a motor-driven syringe pump. During the second hour, the glucose infusion was continued unchanged but an additional

infusion of (i) quinine dihydrochloride (ACF Chemiefarma NV, Maarsse, Holland) $10 \text{ mg base kg}^{-1}$ body weight (BW) dissolved in normal saline solution, (ii) quinidine dihydrochloride (ACF Chemiefarma NV) $10 \text{ mg base kg}^{-1}$ BW in normal saline or (iii) normal saline alone, was given simultaneously. The order of (i), (ii) and (iii) was random in each case.

On each test day, a cannula was introduced retrogradely into a suitable vein on the dorsum of a warmed hand for repeated sampling of arterialised blood. The cannula was kept patent by flushing with small volumes of sterile heparinised normal saline solution. After 15 min bed rest, three basal blood samples (at -10 , -5 and 0 min) were taken. Immediately after the 0 min sample, the glucose infusion was started through a second cannula inserted in an antecubital vein on the opposite arm. Further blood samples were drawn at 50, 55 and 60 min. As soon as the 60-min sample had been taken, one of the infusions (i), (ii) or (iii) above was started in parallel with the dextrose infusion. Further blood samples were taken at 110, 115 and 120 min. Each patient's pulse rate and blood pressure, and an electrocardiograph rhythm strip were taken at 60, 90 and 120 min.

At each sampling time-point, blood was drawn for measurement of plasma glucose (GOD-Perid kit, Boehringer Corporation, Lewes, England), insulin (Albano *et al.*, 1972) and C-peptide (Holman & Turner, 1977) concentrations. In addition, samples were taken for plasma quinine and quinidine assay at 60, 90 and 120 min during infusions (ii) and (iii) respectively. Plasma concentrations of both quinine and quinidine were measured using high performance liquid chromatography as described previously (Karbwang *et al.*, 1989). Concentrations of free drug were also measured in each sample after preparation of a protein-free ultrafiltrate using the Amicon YMT system (Amicon Corporation, Danvers, Massachusetts, USA; Silamut *et al.*, 1985). All samples were taken into heparinised tubes kept on wet ice. Following prompt centrifugation, samples were stored at -70°C and were transported on dry ice before assay.

Mathematical and statistical analysis

To verify that all subjects exhibited normal glucose tolerance, the average plasma glucose and insulin concentrations achieved over the last 10 min of the first hour of the glucose infusion on each of the three test days were calculated. These concentrations were assessed using the 'Continuous Infusion of

Table 1 CIGMA-derived beta cell function and tissue insulin sensitivity values for the 11 subjects on each of the three infusion days. Data are geometric means and s.d.s

Infusion type	Beta cell function (%)	Tissue insulin sensitivity (%)
Saline alone	109 (67–177)	109 (67–178)
Quinine	108 (64–181)	121 (66–220)
Quinidine	99 (65–152)	106 (61–186)

Glucose with Model Assessment' (CIGMA) technique (Hosker *et al.*, 1985); the values were compared with those predicted from a model of glucose homeostasis based on known physiological data concerned with glucose turnover in different organs and with insulin kinetics in response to glucose. Resulting estimates of beta cell function and insulin sensitivity are relative to normal Caucasian subjects with mean values of 100% for both parameters.

Statistical analysis was by parametric tests (Armitage & Berry, 1987). Baseline, 1 h and 2 h values were taken as the average of the three samples over the 10 min period ending at these three times. All insulin, C-peptide, beta cell function and insulin sensitivity values were log-transformed prior to analysis. Data are reported as means (or geometric means) and s.d.s.

Results

The infusions of quinine and quinidine were well tolerated. No subject developed hypoglycaemia or significant cardiotoxicity during or after any study.

Beta cell function and insulin sensitivity

There were no significant differences between the CIGMA-derived values for either pancreatic beta cell function or tissue insulin sensitivity on the three test days ($F_{2,21} = 0.09$ and 0.06 respectively, $P > 0.90$ in each case; Table 1), and the mean values obtained for both of these parameters were close to 100% on each occasion.

Plasma glucose

The plasma glucose concentrations showed significant changes with time ($F_{2,28} = 108.3$, $P < 0.0001$; Figure 1), with values at 1 h and 2 h which were not significantly different from each

Figure 1 Mean $\pm$ s.d. plasma glucose concentrations during a 2 h infusion of $5 \text{ mg glucose kg}^{-1}$ ideal body weight (IBW) min^{-1} in healthy volunteers, with a simultaneous infusion during the second hour of either (i) quinine $10 \text{ mg base kg}^{-1}$ body weight (BW) quinine (■), (ii) quinidine $10 \text{ mg base kg}^{-1}$ BW (●), or (iii) isotonic saline alone (▲).

other but which were greater than the baseline levels (Newman-Keuls test, $P < 0.05$). There was no significant difference between the plasma glucose concentration profiles during the three different infusion regimens ($F_{2,28} = 1.05$, $P > 0.05$), although there was a tendency for the plasma glucose to decrease during the quinine infusion (mean $\pm$ s.d. $7.9 \pm 0.7 \text{ mmol l}^{-1}$ at 1 h vs mean $\pm$ s.d. $6.6 \pm 1.9 \text{ mmol l}^{-1}$ at 2 h; Figure 1).

Plasma insulin

Plasma insulin concentrations also changed significantly with time ($F_{2,28} = 322.6$, $P < 0.0001$; Figure 2), with geometric mean concentrations at 2 h significantly greater than those at 1 h, and those at 1 h significantly greater than baseline (Newman-Keuls test, $P < 0.05$). There was also a significant difference between the insulin response during the three types of infusion ($F_{2,28} = 12.1$, $P < 0.05$). Quinine provoked significantly greater 2 h plasma insulin concentrations (geometric mean [$-\text{s.d.}-+\text{s.d.}$], $70.9 [43.1-116.6] \text{ } \mu\text{mol l}^{-1}$) than either quinidine ($48.7 [30.5-77.8] \text{ } \mu\text{mol l}^{-1}$) or glucose alone ($27.1 [13.5-54.3] \text{ } \mu\text{mol l}^{-1}$; Newman-Keuls test, $P < 0.05$). In terms of the increment in plasma insulin during the second hour of the study, quinine provoked a geometric mean rise ($47.0 [27.8-79.4] \text{ } \mu\text{mol l}^{-1}$) which was over twice that produced by quinidine ($19.8 [6.1-65.2] \text{ } \mu\text{mol l}^{-1}$) and over six times that after glucose alone ($7.5 [0-21.5] \text{ } \mu\text{mol l}^{-1}$; Figure 3).

Figure 2 Geometric mean $\pm$ s.d. plasma insulin concentrations during a 2 h infusion of 5 mg glucose kg^{-1} ideal body weight (IBW) min^{-1} in healthy volunteers, with a simultaneous infusion during the second hour of either (i) quinine 10 mg base kg^{-1} body weight (BW) (■), (ii) quinidine 10 mg base kg^{-1} BW (●), or (iii) isotonic saline alone (▲).

Figure 3 Geometric mean $\pm$ s.d. plasma insulin increments during the second hour of the 2 h infusion period plotted against mean $\pm$ s.d. end-infusion total plasma drug concentrations for quinine (■), quinidine (●) and isotonic saline alone (▲).

Plasma C-peptide

The changes in plasma C-peptide concentrations paralleled those in plasma insulin. There was a significant increase in plasma C-peptide with time ($F_{2,28} = 201.7$, $P < 0.0001$; Figure 4), and a significant difference between the three types of infusion at 2 h ($F_{2,28} = 15.6$, $P < 0.01$). Quinine produced a significantly greater geometric mean concentration (2.45 [1.98–3.03] nmol l^{-1}) than quinidine (1.61 [1.05–2.47] nmol l^{-1}), which, in turn, produced a significantly greater 2 h mean concentration than glucose alone (0.91 [0.59–1.42] nmol l^{-1} ; Newman-Keuls test, $P < 0.05$).

Plasma quinine and quinidine

The plasma quinine concentrations at the end of the quinine infusion (mean $\pm$ s.d. 6.5 ± 4.4 mg l^{-1}) were approximately double the 2 h plasma quinidine concentrations (3.0 ± 0.8 mg l^{-1} , $t = 2.56$, d.f. = 9, $P < 0.05$); a full pharmacokinetic comparison will be published elsewhere. Free quinine concentrations, expressed both as absolute values and as percentages of the total plasma drug concentration (0.55 ± 0.28 mg l^{-1} and $9.4 \pm 2.7\%$, respectively), were significantly lower than those of free quinidine at 2 h (0.91 ± 0.36 mg l^{-1} and $27.8 \pm 11.9\%$, $P < 0.05$ in each case).

Figure 4 Geometric mean $\pm$ s.d. plasma C-peptide concentrations during a 2 h infusion of 5 mg glucose kg^{-1} ideal body weight (IBW) min^{-1} in healthy volunteers, with a simultaneous infusion during the second hour of either (i) quinine 10 mg base kg^{-1} body weight (BW) (■), (ii) quinidine 10 mg base kg^{-1} BW (●), or (iii) isotonic saline alone (▲).

To investigate whether the increment in plasma insulin concentration during the second hour of the study was related to the simultaneous concentration of cinchona alkaloid or to the glucose tolerance of the subject, regression analysis was performed. The independent

associations between plasma insulin increment provoked by the quinine infusion and both tissue insulin sensitivity ($r = -0.495$) and beta cell function ($r = 0.535$) were weak ($0.10 > P > 0.05$ in each case). However, the 2 h total and free plasma quinine concentrations correlated significantly with the insulin increment ($r = 0.662$, $P = 0.028$ and $r = 0.705$, $P = 0.015$ respectively). Stepwise multiple regression analysis revealed that the free quinine concentration was the best predictor of the rise in plasma insulin during the second hour ($t = 2.980$, d.f. = 9, $P = 0.015$); beta cell function and insulin sensitivity were eliminated from the regression equation. There were no statistically significant associations between the second-hour insulin increment during the quinidine infusion and end-infusion total and free drug concentration, beta cell function or tissue insulin sensitivity ($P > 0.10$ in each case).

Discussion

The cinchona alkaloids have been prescribed by physicians for hundreds of years but their effect on blood glucose was not noted until earlier this century (Hughes, 1925). Recent evidence from clinical and laboratory studies has indicated that quinine and quinidine are potent stimulants to the release of insulin from the pancreatic beta cell and, in certain circumstances, hypoglycaemia can result (Harats *et al.*, 1983; Looareesuwan *et al.*, 1985; Okitolonda *et al.*, 1987; White *et al.*, 1983). The mechanism by which quinine provokes insulin secretion is known to be through its ability to mimic the action of glucose on potassium permeability of the beta cell membrane, with subsequent calcium influx (Henquin, 1982; Henquin *et al.*, 1975). The ambient glucose concentration itself has also been shown in *in vitro* studies to modulate the beta cell response to quinine (Henquin, 1982).

Our results confirm that both quinine and quinidine stimulate *in vivo* pancreatic insulin release. However, quinine is a much more powerful stimulus to insulin secretion than quinidine when the two drugs are given in equivalent doses to subjects with confirmed normal glucose tolerance. During the quinidine infusion, plasma insulin concentrations more than doubled relative to the rise in levels when glucose alone was infused over the second hour (see Figures 2 and 3). When quinine was administered, the increase in plasma insulin was more than two-fold that provoked by quinidine and six-fold that when no drug was given. This

apparent difference must, however, be interpreted in terms of the pharmacokinetic properties and plasma protein binding of these diastereoisomers.

Previous studies have shown that quinidine has a greater volume of distribution and is cleared more rapidly than quinine (Jamaludin *et al.*, 1988; White, 1987), with the result that total plasma concentrations for a given dose will be lower. However, the plasma protein binding of quinine is greater than that of quinidine (Ochs *et al.*, 1980; Silamut *et al.*, 1985). Consistent with these observations, the mean total plasma quinine concentration achieved in the present study was approximately double that of quinidine, but free quinine concentrations were significantly lower than those of unbound quinidine. These findings suggest that the drugs have different pharmacodynamic actions on the pancreatic beta cell. Quinine appears a much more potent stimulus to insulin release than quinidine at equimolar tissue concentrations, producing a concentration-dependent response. It is possible that quinidine also stimulates insulin release in a dose-dependent fashion, an association which might have been more obvious if a wider range of free plasma quinidine concentrations (and hence insulin responses) had been obtained.

Two previous studies have examined the plasma insulin response to doses and rates of infusion of quinine (10 mg salt kg^{-1} body weight over 1 h; White *et al.*, 1983) and quinidine (500 mg base over 1 h; Phillips *et al.*, 1986) which were comparable with those employed in the present study. Both of these studies were performed on fasting, nondiabetic Thai subjects who received no co-administered glucose. The arithmetic mean plasma insulin concentration (measured in our laboratory using the same assay technique as in the present study) increased from 8.1 to 16.8 $\mu\text{U l}^{-1}$ after quinine (White *et al.*, 1983), and from 6.1 to 10.9 $\mu\text{U l}^{-1}$ after quinidine (Phillips *et al.*, 1986). These data and the results of the present study demonstrate that plasma glucose concentrations are a powerful amplifier of insulin release stimulated by the cinchona alkaloids; elevation of the plasma glucose from fasting to postprandial levels results in considerable increases in insulin concentrations.

A further possible influence on the plasma insulin response to the cinchona alkaloids is the glucose tolerance status of the subject. There were weak associations between the second-hour insulin increment and tissue sensitivity to insulin and pancreatic beta cell function during the quinine infusion. These measures of glucose

tolerance were within Caucasian reference ranges in our urban-dwelling Thai subjects. It is possible that, in stress and disease states, there might be significant alterations in these parameters (such as an adrenaline-mediated decrease in tissue sensitivity to insulin) which, in turn, might change the insulin response to the cinchona alkaloids and hence the risk of hypoglycaemia. The fact that the 2 h plasma glucose concentrations were similar after each of the three infusions despite markedly different simultaneous insulin levels suggests that acute, compensatory changes in tissue insulin sensitivity occur in normal subjects which are well above the plasma glucose range in which usual counterregulatory mechanisms operate. This putative adaptive change in insulin sensitivity might also be abnormal in disease states in which cinchona alkaloids are used as treatment.

Our results suggest that insulin secretion stimulated by quinine is determined by the plasma concentration of the drug and the ambient plasma glucose concentration. Quinidine is a much less potent stimulus to insulin release

at the same tissue concentration, but glucose also amplifies the beta cell response to this drug. Further studies are needed to investigate the possible contribution of the glucose tolerance status of the subject to increases in plasma insulin provoked by the cinchona alkaloids. The effect of resultant relative hyperinsulinaemia on the plasma glucose concentration itself depends on acute changes in tissue insulin sensitivity which can be independent of the effects of counterregulatory hormones. These observations are of relevance in clinical situations where hypoglycaemia is thought to occur as a result of quinine or quinidine treatment, and should be borne in mind by the physician when planning changes in management.

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References

- Albano, J. D. M., Ekins, R. P., Maritz, G. & Turner, R. C. (1972). A sensitive, precise radioimmunoassay of serum insulin relying on charcoal separation of bound and free hormone moieties. *Acta Endocrinol. (Copenh.)*, **70**, 487–509.
- Armitage, P. & Berry, G. (1987). *Statistical methods in medical research*. Oxford: Blackwell Scientific Publications.
- Bunnag, D. & Harinasuta, T. (1986). The current status of drug resistance in malaria. In *Parasitology Quo Vadis*, ed. Howell, M. J., Australian Academy of Science, pp. 180–196.
- Chongsuphajaisiddhi, T., Sabcharoen, A. & Attanath, P. (1981). *In vivo* and *in vitro* sensitivity of falciparum malaria to quinine in Thai children. *Ann. trop. Paediat.*, **1**, 21–26.
- Fletcher, W. (1925). Further notes on the treatment of malaria with cinchona febrifuge, quinidine and cinchonine. *Bulletins from the Institutes of medical Research, Federated Malay States*. Government Printing Office, Kuala Lumpur, No. 3.
- Harats, N., Ackerman, Z. & Shalit, M. (1984). Quinine-related hypoglycemia. *New Engl. J. Med.*, **310**, 1331.
- Henquin, J.-C. (1982). Quinine and the stimulus-secretion coupling in pancreatic beta cells: Glucose-like effects on potassium permeability and insulin release. *Endocrinology*, **110**, 1325–1332.
- Henquin, J.-C., Horemans, B., Nenquin, M., Verniers, J. & Lambert, A. E. (1975). Quinine-induced modifications of insulin release and glucose metabolism by isolated pancreatic islet cells. *FEBS Lett.*, **57**, 280–284.
- Holman, R. R. & Turner, R. C. (1977). Diabetes: The quest for basal normoglycaemia. *Lancet*, **i**, 469–474.
- Hosker, J. P., Matthews, D. R., Rudenski, A. S., Burnett, M. A., Darling, P., Bown, E. G. & Turner, R. C. (1985). Continuous infusion of glucose with model assessment (CIGMA): Measurement of insulin resistance and beta cell function in man. *Diabetologia*, **28**, 401–411.
- Hughes, T. A. (1925). Effects of quinine on the sugar of the blood. *Indian J. med. Res.*, **13**, 321–326.
- Jamaludin, A., Mohamed, M., Navaratnam, V., Mohamed, N., Ykeoh, E. & Wernsdorfer, W. (1988). Single-dose comparative kinetics and bioavailability study of quinine hydrochloride, quinidine sulfate and quinidine bisulfate sustained-release in healthy male volunteers. *Acta Leidensia*, **57**, 39–46.
- Karbwang, J., Na Bangchang, K., Molunto, P. & Bunnag, D. (1989). Determination of quinine and quinidine in biological fluids by high performance liquid chromatography. *Southeast Asian J. trop. Med. Pub. Hlth*, **20**, 65–69.
- Looareesuwan, S., Phillips, R. E., White, N. J., Kietinun, S., Karbwang, J., Rackow, C., Turner, R. C. & Warrell, D. A. (1985). Quinine and severe falciparum malaria in late pregnancy. *Lancet*, **ii**, 4–8.
- Metropolitan Life Assurance Company. (1959). Net weight standard for men and women. *Stat. Bull. metrol. Life Found.*, **40**, 1–4.
- Miller, K. D., Greenberg, A. E. & Campbell, C. C. (1989). Treatment of severe malaria in the United States with a continuous infusion of quinidine

- gluconate and exchange transfusion. *New Engl. J. Med.*, **321**, 65–70.
- Ochs, H. R., Greenblatt, D. J. & Woo, E. (1980). Clinical pharmacokinetics of quinidine. *Clin. Pharmacokin.*, **5**, 150–168.
- Okitolonda, W., Delacollette, C., Malengreau, M. & Henquin, J.-C. (1987). High incidence of hypoglycaemia in African patients treated with intravenous quinine for severe malaria. *Br. med. J.*, **295**, 716–718.
- Phillips, R. E., Looareesuwan, S., White, N. J., Chanthavanich, P., Karbwang, J., Supanaranond, W., Turner, R. C. & Warrell, D. A. (1986). Hypoglycaemia and antimalarial drugs: Quinidine and release of insulin. *Br. med. J.*, **292**, 1319–1321.
- Sanders, J. P. & Dawson, W. T. (1932). Efficacy of quinidine in malaria. *J. Am. med. Ass.*, **99**, 1773–1777.
- Silamut, K., White, N. J., Looareesuwan, S. & Warrell, D. A. (1985). Binding of quinine to plasma proteins in falciparum malaria. *Am. J. trop. Med. Hyg.*, **34**, 681–686.
- White, N. J. (1985). Clinical pharmacokinetics of the antimalarial drugs. *Clin. Pharmacokin.*, **10**, 55–90.
- White, N. J. (1987). The pharmacokinetics of quinine and quinidine. *Acta Leidensia*, **55**, 65–76.
- White, N. J., Warrell, D. A., Chanthavanich, P., Looareesuwan, S., Warrell, M. J., Krishna, S., Williamson, D. H. & Turner, R. C. (1983). Severe hypoglycaemia and hyperinsulinaemia in falciparum malaria. *New Engl. J. Med.*, **309**, 61–66.
- World Health Organization Malaria Action Programme. (1986). Severe and complicated malaria. *Trans. Roy. Soc. trop. Med. Hyg.*, **80**, (Suppl.), 3–50.

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